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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,351	11/09/2001	David A. Brake	PC9898B	4450

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PFIZER INC
150 EAST 42ND STREET
5TH FLOOR - STOP 49
NEW YORK, NY 10017-5612

EXAMINER
GRASER, JENNIFER E

ART UNIT	PAPER NUMBER
1645	

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7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/036,351	Applicant(s) Brake et al.
	Examiner Jennifer Graser	Art Unit 1645

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Amendt. C, 5/7/03*

2a)☒ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-38 and 52-54* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-38 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some* c)☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted 5/9/03, Paper No. 6C is made. Claims 29-38 and 52-54 are currently pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 53 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 53 is vague and confusing because the claim recites that the homogenate is "a whole cell preparation of *Neospora*". It is unclear if the claim is intended to comprise whole cells or disrupted whole cells. The wording of the claim makes it sound as if the homogenate, is in fact, whole cells, i.e., the' homogenate is a whole cell preparation' , yet the term 'homogenate' implies that the cells are disrupted (as recited in claim 54). Clarification is requested.

Claim Rejections - 35 USC § 112-Scope of Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

> make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 29-38 and 52-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for protecting a mammal against neosporosis, comprising administering to the mammal a vaccine comprising an immunologically effective amount of a *Neospora* homogenate as prepared in Example 1 of the specification, i.e., Neospora antigen (NSA) preparation, and a veterinarily acceptable carrier, does not reasonably provide enablement for "a method for protecting a mammal against neosporosis, comprising administering to the mammal a vaccine comprising an immunologically effective amount of a homogenate prepared from cells of *Neospora*, which homogenate is capable of inducing a protective response against neosporosis in a mammal, and a veterinarily acceptable carrier". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. .

The prior art teaches that it is extremely unpredictable to treat or prevent neosporosis in mammals. Further, the prior art specifically teaches that the use of homogenates prepared from cells of *Neospora*, as recited in the claims, can be used to induce neosporosis in mammals. Numerous prior art references teach that homogenates prepared from *Neospora* tachyzoites and cells infected with *Neospora* tachyzoites can successfully reproduce *Neospora* infection and death in mammals. See Barr et al. J.Vet Diagnosis. 1993. 6(2): 7308; Lindsay et al. Am.J.Vet Res., 1995. 56(9): 1176-1180; and Lindsay et al. J.Parasitol. 1990. 76(3): 410-413, for example.

The vaccine recited in the instantly claimed methods does not distinguish over the homogenates used in these prior art references which actually induce, not protect against, neosporosis. Accordingly, the current scope of the claims is not enabled for methods of protecting against neosporosis.

However, Applicants have found that preparing homogenates from *Neospora* tachyzoites and/or cells infected with *Neospora* tachyzoites and subjecting them to protease inhibitor stocks as described in Example 1, see page 15, lines 10-29, resulted in a unique *Neospora* antigen (NSA) preparation that did not contain any viable tachyzoites. Applicants have demonstrated that the use of this preparation conferred immune protection in mammals challenged with *N.caninum.* The specification does not teach that any other homogenate, antigen or preparation can protect mammals against neosporosis, i.e. the use of 'an homogenate prepared from cells of *Neospora'*, 'a homogenate prepared from tachyzoites', are not enabled. The distinguishing characteristics of Applicants' homogenate must be incorporated into the claims. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims.

In summary, the prior art teaches that it is extremely unpredictable to make and use a vaccine capable of conferring protection against neosporosis. The prior art teaches that homogenates prepared from *Neospora* cells and tachyzoites actually induce disease and are, for the most part, fatal. Applicants' unique preparation which differs from that taught in the prior art

refernces is what has provided the satisfactory results. Claims should be drafted to include this novel scope which would distinguish over the homogenate *Neospora* preparations recited in the prior art.

Response to Applicants' arguments:

Applicants argue that the preparation recited in their claim differs from the prior art compositions taught by the references Barr et al (1993), Lindsay et al (1995) and Lindsay et al (1990) cited in the enablement rejection set forth above. This has been fully and carefully considered but is not deemed persuasive. Claim 29 recites a "homogenate prepared from cells of *Neospora"*. The homogenates prepared by Barr and Lindsay are "homogenates prepared from cells of *Neospora*". Cells containing *Neospora* were homogenized. The scope of claim 29 is so broad as to read on homogenizing cells containing tachyzoites, i.e., cells containing *Neospora* cells which are homogenized. Applicants arguments are not commensurate in scope with the claimed invention. They argue that their homogenate is first prepared by freeing tachyzoites from an infected host cell culture and then disrupting the free (and viable) tachyzoites. This is not what is instantly claimed. Claim 29 does not require the tachyzoites to first be removed from the host cell and then homogenized. A"homogenate prepared from cells of *Neospora"* reads on homogenizing host cells which comprise cells of *Neospora*. Additionally, there is no limitation that no viable cells be included in the preparation.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

6. Claims 29-32, 34-38 and 52-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Conrad et al (WO 95/25541).

Conrad et al teach a homogenate prepared from a culture of biologically pure, isolated bovine *Neospora* tachyzoites (abstract, page 4, lines 1-13, page 8, lines 5-15, especially page 23, lines 20-22). It is specifically taught that this homogenate could be used for the prevention of Neospora infections, i.e., neosporosis. Conrad et al specifically teach administering to a mammal an effective amount of the *Neospora* vaccine in order to treat or prevent an infection caused by *Neospora*. Page 53, lines 17-20, specifically recite that "this is the first experiment to show that cattle can be protected against *Neospora* abortion by immunization with culture-derived tachyzoites of the BPA-1 *Neospora* isolate". Neosporosis is a major cause of abortion. The homogenate of Conrad et al specifically binds to the sera obtained from the cows infected with *Neospora* tachyzoites and the uninfected calves (Material and methods, and Results). The specific binding between the homogenate and the sera indicate that the homogenate contains antigens that have induce an enhanced antibody response in the tested animals. Conrad et al

teach that a vaccine comprising a crude extract of *Neospora* tachyzoites, bradyzoites or other stages may be used. See page 23, lines 20-21. Conrad et al also teach that the homogenate from a crude extract of isolated bovine *Neospora* tachyzoites has the same antigenic components present in *Neospora caninum* NC-1. See page 33, lines 23-30 and Tables 1-2. Therefore, the homogenate prepared from a crude extract of isolated bovine *Neospora* tachyzoites BPA1 and BPA2 has equivalent antigenic components to the homogenate prepared from *Neospora caninum* NC-1 tachyzoites. Conrad further teach that the homogenate can be used with additional immunomodulatory components, such as oil-in-water emulsion, various adjuvants or cytokine (page 22, lines 1-23). The reference also teaches that the vaccine/homogenate preparation can be an attenuated *Neospora* vaccine or an antigen produced by recombinant technology. Lastly, Conrad et al teach that the vaccine/homogenate preparation can be combined with other virus or bacterial endotoxins capable of inducing a protective response against a disease or pathological condition (page 22, lines 1-2).

Applicants' specification defines homogenate" as "a preparation prepared by homogenizing or disrupting cells of *Neospora"*. They state that "the homogenate may comprise all of the components produced by the homogenization or disruption of whole *Neospora* cells, thus representing a "whole cell" preparation. Alternatively, the homogenate may consist of a fraction of the total contents of the whole cell preparation using one or more fractionation, isolation or purification steps know in the art". See page 9, lines 11-25 of the instant specification. Accordingly, "a crude extract of Neospora tachyzoites" reads on the instant

claims. See page 38, lines 34- page 39, line 5 and especially page 39, line 15-30, of Conrad which teaches that parasites were harvested, cells were disrupted, the suspension was passed through a filter to remove cellular debris and tachyzoites were pelleted by centrifugation. After removing the supernatant, the pellet was washed in buffer and resuspended in modified PBS (lines 1-30). This method clearly meets Applicants' definition of a homogenate produced by disruption of whole cells of Neospora tachyzoites. Additionally, the methods which use fractions and antigens prepared from the homogenates disclosed by Conrad also anticipate the claims because the specifications definition of 'homogenate' includes "a fraction of the total contents of the whole cell preparation using one or more fractionation, isolation or purification steps know in the art".

Response to Applicants' Arguments:

Applicants argue that "homogenate" is defined in their specification as a preparation obtained by homogenizing or disrupting whole cells of *Neospora*. They argue that Conrad teaches homogenizing host cells comprising *Neospora* and not whole cells of *Neospora*. This argument has been fully and carefully considered but is not commensurate in scope with the claimed invention. Claim 29 does not require the tachyzoites to first be removed from the host cell and then homogenized. A"homogenate prepared from cells of *Neospora"* reads on homogenizing host cells which comprise cells of *Neospora*. Additionally, there is no limitation that no viable cells be included in the preparation. The claim does not require that the tachyzoites

be removed from the infected host cell culture prior to the homogenization. The claim reads on tachyzoites which are homogenized while still in the host cell.

Applicants further argue that Conrad et al do not define what is meant by "a crude extract of isolated bovine *Neospora* tachyzoites". Conrad et al teach a homogenate from a crude extract of isolated bovine *Neospora* tachyzoites has the same antigenic components present in *Neospora caninum* NC-1. Vaccine comprising a crude extract of *Neospora* tachyzoites, bradyzoites or other stages is taught on page 23, lines 20-21. Conrad teaches that it is desirable to just use antigens or extracts taken from *Neospora* cells to insure that infection does not occur. See page 38, lines 34- page 39, line 5 and especially page 39, line 15-30, of Conrad which teaches that parasites were harvested, cells were disrupted, the suspension was passed through a filter to remove cellular debris and tachyzoites were pelleted by centrifugation. After removing the supernatant, the pellet was washed in buffer and resuspended in modified PBS (lines 1-30). This method clearly meets Applicants' definition of a homogenate produced by disruption of whole cells of Neospora tachyzoites. Additionally, Conrad's methods which use fractions and antigens prepared from the homogenates disclosed by Conrad also anticipate the claims because the specifications definition of 'homogenate' includes "a fraction of the total contents of the whole cell preparation using one or more fractionation, isolation or purification steps know in the art". See page 9, lines 15-20, of the instant specification which recites: "Alternatively, the homogenate of the present invention may consist of a fraction of the total contents of homogenized or disrupted Neospora cells, which fraction is prepared from the whole cell preparation using one or

more fractionation, isolation or purification steps known in the art including, e.g., centrifugation, filtration, dialysis, preparative gel electrophoresis, affinity chromatography, ion exchange chromatography, size exclusion chromatography, ammonium sulfate precipitation, or some combination thereof..".

7. Claims 29-32, 34-38 and 52-54 are rejected under 35 U.S.C. 102(e) as being anticipated by Conrad et al (5,889,166).

Conrad et al teach pharmaceutical compositions for the treatment and prevention of Neospora infections (abstract). The reference discloses that a "biologically pure bovine Neospora culture" refers to a continuous in vitro culture of bovine Neospora organisms (e.g. tachyzoites) which is substantially free of other organisms other than the host cells in which Neospora tachyzoites are grown (col. 2, lines 42-45). Vaccines may comprise a crude extract of Neospora tachyzoites (column 12, lines 51-52). The homogenate prepared from a crude extract of isolated bovine *Neospora* tachyzoites BPA1 and BPA2 has equivalent antigenic components to the homogenate prepared from *Neospora caninum* NC-1 tachyzoites. It is specifically disclosed that "cows infected using culture-derived tachyzoites mount a protective immune response and prevent transplacental infection of the fetus (col. 11, lines 60-65 and col. 28, lines 1-4). Column 11, lines 65 through column 12, lines 1-20, recite that the vaccines may comprise one or more immunomodulatory components, such as adjuvants or cytokines which include interleukin-1, 2 and gamma. The vaccines are designed to be given to cattle and other animals (col. 12, lines 39-42).

Response to Applicants' Arguments:

Applicants argue that "homogenate" is defined in their specification as a preparation obtained by homogenizing or disrupting whole cells of *Neospora.* They further argue that the protection of cows against *Neospora* infection was achieved with live, infectious, unattenuated tachyzoites. Lastly, they argue that although Conrad teaches that the *Neospora* vaccines may comprise a crude extract of *Neospora* tachyzoites the patent does not teach how to prepare and use such an extract. These arguments have been fully and carefully considered but are not deemed persuasive.

Conrad et al teach that the *Neospora* vaccines may comprise a crude extract of *Neospora* tachyzoites. It is disclosed that preferred vaccines comprise partially or completely purified Neospora protein preparations. See column 12, lines 50-59. Conrad's methods which use fractions and antigens prepared from the homogenates disclosed by Conrad anticipate the claims because the specifications definition of 'homogenate' includes "a fraction of the total contents of the whole cell preparation using one or more fractionation, isolation or purification steps know in the art". These extracts and protein fractions read on the term 'homogenate' in claim 29.

With respect to Applicants' argument that the protection of cows against *Neospora* infection was achieved with live, infectious, unattenuated tachyzoites, Conrad et al specifically teach that an attenuated Neospora vaccine can only be used in the absence of a risk of human infection. Thus, preferred vaccines are subunit vaccines that elicit antibody and cell-mediated (CMI) immunity to antigens of bovine Neospora. See column 11, col.1, lines 50-55. Since the

specification defines "homogenate' as "a fraction of the total contents of the whole cell preparation using one or more fractionation, isolation or purification steps know in the art". These extracts and protein fractions read on the term 'homogenate' in claim 29. See page 9, lines 15-20, of the instant specification which recites: "Alternatively, the homogenate of the present invention may consist of a fraction of the total contents of homogenized or disrupted Neospora cells, which fraction is prepared from the whole cell preparation using one or more fractionation, isolation or purification steps known in the art including, e.g., centrifugation, filtration, dialysis, preparative gel electrophoresis, affinity chromatography, ion exchange chromatography, size exclusion chromatography, ammonium sulfate precipitation, or some combination thereof..". The antigen and protein extract preparations prepared from Neospora cells and used as vaccines clearly read on the scope of the claims. Applicants' arguments are not commensurate in scope with the claimed invention and the claims remain rejected.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J Graser 7/1/03

JENNIFER E. GRASER
PRIMARY EXAMINER